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10/540,336	01/10/2006	Cornelis Marius Timmers	2002.750US	8846

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
11/05/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/540,336	TIMMERS ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-13 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 4-13, 16 are pending in the current application.

2. This application is a national stage of PCT/EP03/51025 filed November 16, 2003 which claims priority to U. S. Provisional Application 60/435,040 filed December 20, 2002 and European Union Application (EPO) 2102866.7, filed December 20, 2002.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 18, 2008 has been entered.

Response to Arguments

3. Applicant's arguments filed August 18, 2008 have been fully considered but they are not persuasive. The provisional 103(a) rejection is withdrawn based on applicants' representatives statement under 103(c). The rejections for enablement are maintained as the directions for the preparation and function of all the scope of "heteroaryl" moiety is not enabled. The number of examples provided by the specification are few and have been discussed previously (and are reproduced here again). It would appear that the applicant is arguing that essentially any molecule, can be made without undue experimentation. This is in fact not the situation in the chemical arts. Contrary to the assertion at pg. 6 that " for each of the possible substituents for R4 and R5 of the claimed tetrahydroquinoline derivatives of formula I at least one representative example is provided in the currently pending application.", the examples provided are not

representative. In fact on R4 the only groups shown are OMe, OH and H. R6 is only ever phenyl, furan and thiophene. R5 is the only group that has any significant variation and the examiner is only taking issue with the R7 "heteroaryl" and the R8 and R9 "heterocycloalkyl", which have been disclosed as phenyl, pyridine, furan, and isoxazole in the former and piperazine, pieridine, morpholine and pyrrolidine in the later. The examiner (*vide infra* and in the previous action) serve to show the scope that is enabled by the specification, in terms of the compounds of synthetic chemistry, and the teaching of the art in terms of the unpredictability in FSH receptor ligand development. The disclosure of a few examples of "heteroaryl" does not enable all "heteroaryl" or "heterocyclic" on R6 and R5 (which is nested to R7, which is in turn nested to R8 and R9). A narrowing of the claim language on "heterocycloalkyl" and "heteroaryl" would obviate the rejection.

The rejection of the method claim 16 for lack of enablement with respect to the "methods of fertility regulation" is maintained, however the examiner would like to extend the discussion further. In light of the data submitted in the declaration by Mr. Timmers, it is clear that some of the compounds are agonists and some are antagonists and others appear to be partial agonists. The confusion by the examiner was with respect to the nebulous statements of Example 51. It is of course possible for a partial agonist and to antagonize the FSH ligand resulting in a compound that is both an agonist and antagonist (like compound 25). These behaviors are very complex and as shown by the data vary from compound to compound. Each one of these different pharmacological behaviors may be linked to a distinct outcome on fertility or possibly not. This has not been shown. The applicant is encouraged to continue the work on unraveling the complex pharmacological behavior and its relationship to the treatment of

"fertility regulation". The paucity of data in the specification, the relatively poorly developed understanding of the effect of FSH receptor agonists/antagonists, and the myriad of different physiological functions encompassed by the term "fertility regulation" clearly warrant the conclusion of lack of enablement which was supported by references testifying to the state of the art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 4-13, 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4, 7, 10-21, 23 of copending Application No. 10/482,707. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope substantially and cover the same compounds. The wording is only slightly different and the '707 application is broader

but where X is NH and Y is CO the compounds of the instant case are produced. It is noted that some of the same species are present in both applications.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Van Straten et. al. teaches numerous compounds of the instant case that amount to change of the position of substituents, or other minor variations available within the general teaching.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Van Straten et. al. evidently do not expressly teach the compounds of the instant case, based on a proviso, but the general teaching provides the compounds of the instant case that are only minor variations.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In*

re Bode 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. The applications appear to have a common assignee.

6. Claims 1, 4-13, 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 11 of copending Application No. 10/540,335. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope substantially and cover the same compounds. The wording is only slightly different and the '335 application is narrower but the genus produced is nearly identical. It is noted that some of the same species are present in both applications.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4-13, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, does not reasonably provide enablement for the full scope of "heteroaryl" of R6 and R7 nor the full scope of "heterocycloalkyl" of R8 and R9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing all heterocycles, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist. **(C) The state of the prior art:** Little prior art exists on

these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. **(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** The examiner will first consider the Markush structure I of claim 1, and the inherent limitations of the chemistry used to prepare the examples as well as starting materials and then address the influence of these groups on the utility.

As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

While a vast array of anilines are commercially available for the Skraup reaction. The substituents R5 apparently has enormous permutations due to their apparent identity as R7 which is actually a list of 10 groups which then further contain the groups R8 and R9 which are themselves more than six groups. Where can one purchase or prepare the required anilines

possessing these groups? While apparently a Lewis acid catalyzed version of the Skraup reaction is used to construct the quinoline nucleus, the Skraup has been shown to be sensitive to substituents on the starting aniline (The Chemistry of Heterocyclic compounds: Quinolines PART 1, Jones, Gurnos editor Wiley: New York, 1977 pg. 104-117.) For example the claims are drawn towards "carbonyloxy" groups which are esters and these groups are "susceptible to decarboxylation" a "further disadvantage" (Jones, ibid. pg. 104 at b.). "Other groups that are modified or eliminated during a Skraup synthesis are the sulphonic acid group, and ether or ester groups." *p*-acetylaniline also fails to undergo the reaction (Jones ibid. pg. 105). One very serious problem is the formation of regioisomeric 5 and 7 quinolines when using meta-substituted anilines, which may or may not be separable.

While some of these limitations are clearly synthetic, perhaps more importantly are the requirements for activity at the FSH receptor. The only information as to what these compounds are doing in the pharmacological sense is the following statement: "Compounds of all examples exhibited an EC50s (IC50s0) value of less than 10^{-5} M in either an agonistic or antagonistic assay set-up or both." The data submitted in the affidavit shows that some compounds bind the receptor, however the working examples are not commensurate in scope to that which is claimed. The state of the art in FSH receptor ligands shows that activity is highly dependent upon structure. See: Nicole C. R. van Straten, Twan H. J. van Berkel, Dennis R. Demont, Willem-Jan F. Karstens, Remco Merkx, Julia Oosterom, Jurgen Schulz, Richard G. van Someren, Cornelis M. Timmers, and Peter M. van Zandvoort "Identification of Substituted 6-Amino-4-phenyltetrahydroquinoline Derivatives: Potent Antagonists for the Follicle-Stimulating Hormone Receptor" Journal of Medicinal Chemistry **2005**, *48*, 1697-1700, In particular pg. 1698

"Aromatic susbstituents in position 6 [R_6 of the instant claims] are preferred..." It is further stated that there is an apparent size constraint on substituents, "space is limited because introduction of an extra t-butyl group in **11** led to a drop in potency".

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

8. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to "methods of fertility regulation", however no clear nexus exists between the compounds described here and "methods of fertility regulation". In the words of van Straten et. al. (ibid. pg. 1700 conclusion) these compounds "may serve as starting points for further optimization to evaluate the feasibility of FSH receptor antagonists as a novel method for contraception."

The effect physiologically of a compound that binds and perturbs the FSH-R (a GPCR) is unclear. While knockout mice are clearly sterile ("Genetic elimination of the alpha subunit in mice by homologous recombination (7) causes complete deficiency of all three glycoprotein hormones, and animals of both sexes are not only sterile but also hypothyroid." M. Ram Sairam

and Hanumanthappa Krishnamurthy "The Role of Follicle-Stimulating Hormone in Spermatogenesis: Lessons from Knockout Animal Models" Archives of Medical Research 32 (2001) 601–608.) Mutants which presumably have some receptor function (as in the instant case) "exhibit delayed sexual maturity and reduced fertility". The real problem here is that this receptor is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor.....**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore, this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation..... Ligand activities that are not related to a standard G-protein-mediated physiological response **might have therapeutic utility**.

Here we have exactly this situation, namely a ligand with affinity, and very limited information about the function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility."

FSH receptor signaling is very complex as evidenced by Alfredo Ulloa-Aguirre et. al. "Role of the intracellular domains of the human FSH receptor in GαS protein coupling and receptor expression." *Molecular and Cellular Endocrinology* **2007**, 260–262, 153–162.

"The human FSHR consists of 695 amino acids (the first 17 amino acids encoding the signal sequence) (Simoni et al., 1997; Ulloa-Aguirre and Timossi, 1998; Dias et al., 2002); upon

activation by agonist, the activated receptor may trigger activation of a number of intracellular signaling pathways. In the classical, linear signaling cascade, occupancy of the FSHR causes activation of the heterotrimeric Gs protein, which in turn stimulates the effector adenylyl cyclase with the consequent increase in the synthesis of the second messenger cAMP, activation of PKA, phosphorylation of cAMP response element-binding protein, and activation of transcription (Reichert and Dattatreyamurty, 1989). Nevertheless, **increasing evidence indicates that in addition to the adenylyl cyclase/cAMP/PKA signaling pathway, activation of the FSH receptor by its cognate ligand also triggers activation of other intracellular signaling cascades, including the MAPK and PI3-K/Akt pathways** (Cameron et al., 1996; Maizels et al., 1998; Gonzalez-Robayna et al., 2000; Richards et al., 2002; Seger et al., 2001)..... **In contrast to the related TSHR and LHR, there is a paucity of structure-function data on the role of the intracellular domains in FSHR-mediated signal transduction** and receptor expression."

"Although the hFSHR preferentially couples to the Gsα-subunit, there is some experimental evidence suggesting that the FSHR may additionally signal through the pertusis toxin-sensitive Gi/o-mediated pathways (Eskola et al., 1994; Arey et al., 1997; Timossi et al., 1998). In this regard, alternative spliced variants of the receptor may be one of the mechanisms by which particular intracytoplasmic domains of the FSHR may signal through these G proteins (Sairam et al., 1997). As mentioned above, the FSHR also signals through cAMP- dependent, but PKA-independent alternate signaling cascades (Richards et al., 2002); in addition, it has been shown that the adapter protein 14-3-3τ, a member of the 14-3-3 protein family which play a key role in signal transduction pathways, cell division and apoptosis (Tzivion and Avruch, 2002), interacts with the iL2 of the hFSHR, suggesting a role for this cytoplasmic protein in FSHmediated cAMP independent signaling (Cohen et al., 2004). APPL1, another adapter protein that interacts with the p110α catalytic subunit of PI3K and with inactive Akt (Mitsuuchi et al., 1999), has been more recently identified as an hFSHR iL1-interacting partner, providing a potential link between the FSHR and the PI3K/Akt signaling pathway (Nechamen et al., 2004). One thus may envision a complex system of multiple, pleiotropic signals triggered by the activated FSHR, in which compartmentalization and oligomerization of particular receptor populations may potentially play fundamental roles." Pg. 159

One reviewer summarized the state of the art this way: Only in the clinic will the question of whether small molecule LHR and FSHR modulators will be successful as fertility-regulating agents be answered." (Guo, Tao "Small molecule agonists and antagonists for the LH and FSH receptors." Expert Opinion on Therapeutic Patents 2005 15(11) 1555-1564, conclusions.) See the MPEP 2164.02 for the correlation of in-vitro to in-vivo testing. There is no successful use of

these compounds in an animal model and no clear correlation between antagonism of this receptor and a therapeutic outcome, thus undue experimentation would be required.

Conclusion

9. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625